REMARKS

Claims 1 – 14 and 24 – 32 are pending in the application. Claims 1 – 9, 11, 13, and 24 – 32 are rejected under 35 U.S.C. § 112, first paragraph, as having inadequate written description. Claims 5, 9, 13, 14 and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1 – 9, 11, 13, and 24 – 32 are rejected under 35 U.S.C. § 103(a), as being obvious over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,471. Applicants gratefully acknowledge that claims 10 and 12 would be allowable if written in independent form including all of the limitations of the base claim and any intervening claims.

Applicants have amended the claims under consideration to more clearly define and distinctly characterize Applicants' novel invention. The amendments presented herein contain no new matter.

Applicants respectfully request entry and consideration of the foregoing remarks, which are intended to place this case in condition for allowance.

I. The Specification Provides Adequate Written Description for Claims 1 – 9, 11, 13, and 24 – 32

At page 2, paragraph 2 of the instant Office Action, claims 1 – 9, 11, 13, and 24 – 32 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to those skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

There is a strong presumption that claims as originally filed meet the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner states that adequate written description of the claimed oligonucleotides is provided in the as-filed specification to the extent the claimed oligonucleotides are complementary to a target portion of the nucleic acid sequence of human angiogenin set forth in Figure 1. This nucleic acid sequence was known before the filing date of the present application. Presumably, if claim 1 were restricted to the nucleic acid sequence of Figure 1, the written description rejection would be overcome, because one of skill in the art would understand that the claimed complementary oligonucleotides could be identified based on the known nucleic acid sequence through routine efforts, experimental or otherwise. Stated differently, one of skill in the art could precisely envision the structures of all oligonucleotides of claim 1.

The Examiner states that the specification is deficient to the extent that one of skill in the art would not understand that the applicants were in possession of the invention to the extent that the claim term "nucleic acid encoding human angiogenin" includes polymorphic, splice and allelic variants of human angiogenin and that applicants have not disclosed specific sequences for these variants. However, it is black letter patent law that the written description requirement does not require the applicant to describe in the specification exactly the subject matter claimed. Instead, the description must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. Well known information need not be repeated in the specification.

Importantly, the Examiner recognizes that one of skill in the art would understand that the term "nucleic acid encoding human angiogenin" includes polymorphic, splice and allelic variants of human angiogenin. The issue presented by the Examiner is whether specific nucleic

acid sequences need be identified for each polymorphic, splice or allelic variant of human angiogenin to meet the written description requirement for the claimed complementary oligonucleotides. Applicants respectfully submit that no such disclosure is required.

The subject matter of claim 1 is directed to oligonucleotides complementary to nucleic acid sequences, and not to any particular nucleic acid sequence *per se*. Claim 2 further requires that the oligonucleotides bind to the target portion of the nucleic acid in a manner to inhibit the expression of angiogenin, and so would not encompass any and all complementary oligonucleotide sequences.

Applicants' specification when combined with the knowledge of one of skill in the art meets the written description requirement by demonstrating that applicants had possession of the claimed invention. Applicants disclose the nucleotide sequence of the human angiogenin gene at Figure 1. Applicants disclose specific oligonucleotides that inhibit the expression of the human angiogenin gene depicted at Figure 1. Applicants also disclose, at page 41, lines 16 – 18, that "additional oligonucleotides within the scope of this invention can be prepared by first selecting a target sequence anywhere along the known nucleic acid sequence of the angiogenin gene." Applicants further disclose that the complete gene sequences for certain mammalian angiogenins are known and that oligonucleotides hybridizable with any portion of the gene sequence or the mRNA transcript may be prepared by the oligonucleotide synthesis methods known to those skilled in the art. (Page 30, lines 14 – 17.). As the Examiner points out, one of skill in the art would understand that the claim term " nucleic acid encoding human angiogenin" includes polymorphic, splice and allelic variants. One of skill in the art would not be prohibited, and in fact would be encouraged, to look to readily available literature references for published nucleic acid sequences for polymorphic, splice and allelic variants or to methods for identifying such

variants. Once identified, whether by literature as with the sequence in Figure 1 or by sequencing methods, the specification teaches how one of skill in the art can prepare complementary oligonucleotides and how to determine whether the oligonucleotides bind to the target portion of the nucleic acid in a manner to inhibit the expression of angiogenin. Accordingly, one of skill in the art, based on the specification and her own knowledge, could precisely envision the structures of all oligonucleotides of claim 1, and especially the oligonucleotides of claim 2 that are limited to those that inhibit the expression of angiogenin and not all complementary oligonucleotides.

Regarding the new matter rejection, the term "OCH_3CH_3" was a typographic error and has been deleted from claim 29. The term "OCH_2OCH_3" has been added to claim 29 to replace "OCH_3CH_3" and support for "OCH_2OCH_3" can be found in claim 9 as originally filed.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 1 – 9, 11, 13, and 24 – 32 under 35 U.S.C. § 112, first paragraph.

II. Claims 5, 9, 13, 14, and 29 Are Definite

At page 4, paragraph 3 of the instant Office Action, claims 5, 9, 13, 14, and 29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The Examiner is of the opinion that claims 5, 9, 13, 14, and 29 fail to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner states that claim 5 is vague and indefinite because "modified internucleotide linkage" is recited to encompass a "phosphodiester" linkage, which is a naturally occurring and not a modified linkage. In response, Applicants have amended claim 5 to remove the term "phosphodiester".

The Examiner also asserts that claim 5 recites the term "CH_3-O-N(CH_3)-CH_2," which is chemically improper and suggests amending the claim to recite "CH_2-O-N(CH_3)-CH_2." In response, applicants have amended the claim in accordance with the Examiner's suggestion.

The Examiner asserts that claim 9 recites the phrase "substituted silyl: an RNA cleaving group: a cholesteryl group...." which is indefinite due to the presence of the colon. In response, Applicants have amended the phrase to substitute a semi-colon for the colon. Applicants respectfully submit that claim 9 as amended is definite.

The Examiner asserts that claims 13 – 14 contain the chemically improper terms "OCH_3OCH_3" and "$OCH_3O(CH_2)_pCH_3$" and suggests amending the claims to recite the chemically proper terms "OCH_2OCH_3" and "$OCH_2O(CH_2)_pCH_3$." Applicants have amended the claims as suggested by the Examiner.

The Examiner asserts that claim 29 contains the chemically improper limitations "-OCH_3CH_3" and "$OCH_3O(CH_2)_nCH_3$," and suggests correcting these terms to read "-OCH_2CH_3" and "$OCH_2O(CH_2)_nCH_3$." Applicants amended "-OCH_3CH_3" to recite "OCH_2CH_3" as explained above, and have amended "$OCH_3O(CH_2)_nCH_3$," as suggested by the Examiner. The Examiner further asserts that the recitation in claim 29 of wherein the modified 2' hydroxyl moiety is selected from the group consisting of "OH" is vague and indefinite because "OH" is not a modified hydroxyl moiety. Applicants have deleted "OH" from the claim, thus obviating the rejection.

In view of the above, Applicants respectfully request withdrawal of the rejections of amended claims 5, 9, 13, 14, and 29 under 35 U.S.C. § 112, second paragraph.

III. Claims 1 – 9, 11, 13, and 24 – 32 Are Non-Obvious Over Vallee et al. in View of Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al.

At page 6, paragraph 4 of the instant Office Action, claims 1 – 9, 11, and 13 remain rejected and claims 24 – 32 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,47; for the reasons cited in the office action mailed 3/19/2002. The basis for the Examiner's combination of the cited references and the teachings thereof is fully presented in prior office actions. Applicants' positions are presented in the responses filed September 4, 2002 and April 14, 2003 incorporated herein in their entireties and will not be repeated here for the sake of brevity.

Applicants respectfully traverse the Examiner's rejection. The Examiner is ascribing a teaching to the Olson reference that simply isn't there. The Examiner states that "Olson et al teach the use of antibodies to inhibit the expression of angiogenin." Page 6, paragraph 4 of the Office Action. In fact, Olson et al does not teach the inhibition of the expression of the angiogenin protein by inhibiting the nucleic acid, but rather teaches binding an antibody to the angiogenin protein extracellularly. The angiogenin protein in Olson et al is produced by the cells, excreted outside of the cells, and then bound by the antibody, which may inhibit its activity. In other words, Olson binds the protein. In contrast, Applicants bind the nucleic acid. These are two very different approaches. Olson et al, therefore, provides no motivation to bind the nucleic acid.

Furthermore, Applicants respectfully submit that the cytotoxicity demonstrated by the claimed compounds in terms of data showing an actual decrease in tumor size is an unexpected result favoring non-obviousness. See page 44, lines 7 – 11; page 44, lines 12 – 22, page 46, lines 6 – 21. This is an unexpected result because antisense oligonucleotides are not known to be predictably cytotoxic. Further, Olson et al. teaches that antibodies specific for the angiogenin protein are not cytotoxic to tumor cells and only have the effect of slowing tumor growth. Olson et al concluded that this effect most likely occurs due to the neutralization of the activity of extracellular angiogenin. (page 4576, abstract). Therefore, one having skill in the art would not have expected based on Olson et al. or any of the other combined references that oligonucleotides complementary to nucleic acids encoding angiogenin would have a cytotoxic effect.

In view of the above, Applicants submit that claims 1 – 9, 11, 13, and 24 – 32 are patentable over Vallee et al. in view of Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al., and respectfully request the withdrawal of the rejections of these claims under 35 U.S.C. § 103(a) and allowance of these claims.

IV. Conclusion

Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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